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Review

Prenatal diagnostic advances for fetal skeletal dysplasia: A systematic review

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Abstract
This systematic review discusses several articles for analyzing the prenatal analysis of fetal skeletal dysplasia. This study sheds light on the use of various ways through which analysis of this disease is possible like the use of whole genome sequencing, 3D-CT and many more. The review discusses the critical factors associated with the disease and it provides recent facts and figures to improve the understanding of the disease and the reasons for its development of the disease. It uses a Prisma diagram as well to select the journals based on which the review is done so that the authenticity and reliability of the review remain satisfactory.

Keywords
Fetal Skeletal-Dysplasia, Skeletal Dysplasia, Bone Deformations and Deformed Bones

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Introduction

Fetal Skeletal Dysplasia (FSD) is an osteochondroplasty disease with firm clinical heterogeneity and it affects approximately 2.4 to 4.5 of every 10,000 births. Non-lethal skeletal dysplasia occurs as 1 in every 5,000 births and lethal skeletal dysplasia occurs at the rate of 0.95 to 1.5 per 10,000 births. Chromosomal abnormalities are associated with this disease; however, mutations are mostly related to this disease. As per the opinion of Liu et al. (2022), fetal skeletal dysplasia includes systemic bone disorder or cartilage disorder [1].

De Ponti et al. (2022) mentioned that FSD is a disease that is found among pregnant women, and it is difficult to distinguish these types of diseases in most cases during the fetal period [2]. The prenatal diagnosis of this disorder is presently done by X-ray, ultrasound and "magnetic resonance imaging" [3]. Skeletal dysplasia is identified with the help of routine ultrasound ataround 20 weeks during pregnancy. The rate of prenatal diagnosis of skeletal dysplasia is around 65% [4]. However, these methods are not highly effective and sufficient for the diagnosis of this disease. As a result of difficulties associated with the fetal ultrasonic diagnosis, the diagnosis of the severity of fetal dysplasia seems to be quite difficult. Fetal Magnetic Resonance Imaging (MRI) enables easy analysis of the fetal spines, and soft tissues as well as the detection of the marrow of patients. MRI refers to the medical imaging technique by making use of radiology to form pictures of the anatomy and the physiological processes within the body. In the view of Toscano et al. (2021), ultrasound imaging and MRIs can also reveal amniotic fluid appearances in the brain of the fetuses [5]. This study helps in better understanding the need for the diagnosis of FSD and recent advances for that.

Material and Methods

To gather available and current evidence of prenatal diagnosis for FSD, a systematic review was conducted in line with the PRISMA declaration. The literature search was performed from 2018 to 2022.

Inclusion criteria: Published articles, case reports, crosssectional or designed studies, case-control and cohort studies and randomized clinical trials were included in this review. These articles should be written in English language, accompanied or not, by other languages.

Exclusion criteria: Epidemiological or prevalence studies, congress contributions (presentations, conferences and posters) and reviews were excluded. Articles written other than in the English language are also not included.

Search strategy: The searches were conducted in the following electronic databases: Pubmed-Medline and Cochrane Library. For searching the Web of Science, Science Direct and Google Scholar were also assessed. The search was performed using the following keywords: Fetal Skeletal Dysplasia, Fetal Dysplasia, Fetuses with Deformed Bones, Fetuses with Bone Deformations, Skeletal dysplasia and Diagnosis of Fetal Skeletal dysplasia.

Eligibility criteria: Articles were identified by author and title to eliminate duplication. Relevant publications related to FSD, its symptoms, and management of FSD were chosen using the title, abstract, or from the whole research. The author of this review used this screening method. The author evaluated and thoroughly read the articles that fit the requirements.

Data recording: Data was recorded on the last name of the author and publication year.

Results

Study selection

A total of 70 papers were obtained through a literature search using keywords. Out of 70, 44 similar and duplicate papers were excluded. The number of articles excluded after reviewing abstracts and titles was 20. The papers selected for which full text was managed was 10 (Figure1).

Study characteristics

The primary characteristics of the research that have been incorporated into the review are described in Table 1. All of the selected research was cross-sectional descriptive studies, and their complete texts were available in the English language up until September 2022.

As per the views of Cormier-Daire et al. (2022), a disease of "osteochondrocytes" includes strong levels of clinical variability [6]. The problems associated with this disease are that it leads to a reduction in the bust size. Tian et al. (2020), accuracy in terms of the use of ultrasonic sound in order to detect Skeletal dysplasia is around 40% [7]. Jimah et al. (2021), mentioned that high-quality prenatal imaging can provide specific information so that infants can be diagnosed easily with FSD [8]. It is understood that technological advancement is the means through which the detection of this disease can be done more accurately. Emms et al. (2022), proposed whole exome sequencing for detecting skeletal deformities [9]. It needs to mention that research and development is one of the major means through which the treatment, as well as detection plan for FSD, can be dealt with strong hands [10].

The analysis comes out with the fact that prenatal ultrasonic sound and MRI is used for the detection of this disease widely.

Table 1. Salient features of some studies included in the study.

S. No	Author, Year	Study Design	Intervention
1	Chandler et al. (2018) [20]	Cohort study	Rapid fetal exome sequencing
2	Liu et al. (2019) [21]	Cohort study	Karyotyping, whole genome sequencing, and targeted next-generation sequencing of skeletal disease-related pathogenic genes
3	Waratani et al. (2020) [12]	Cross-sectional study	3D-CT
4	Tian et al. (2020) [7]	Cross-sectional study	Comparing the results of whole-exome sequencing and fetal ultrasound test
5	Yan et al. (2020) [22]	Pilot study	Non-invasive prenatal sequencing for multiple Mendelian monogenic disorders (NIPS-M) among fetuses
6	Mellis et al. (2020) [23]	Retrospective study	Noninvasive prenatal diagnosis (NIPD) for FGFR3-related skeletal dysplasias
7	Tang et al. (2021) [24]	Cross-sectional study	SNP-array and Whole Exome Sequencing
8	Wang et al. (2021) [25]	Cross-sectional study	Non-invasive ampliseq-based targeted sequencing panel by Ion Proton and NextSeq550 instruments
9	Chu et al. (2021) [26]	Case report	Next-generation sequencing for mutations-a novel de novo mutation
10	Liu et al. (2021) [27]	Cross-sectional study	Sonographic examination and gene variation testing

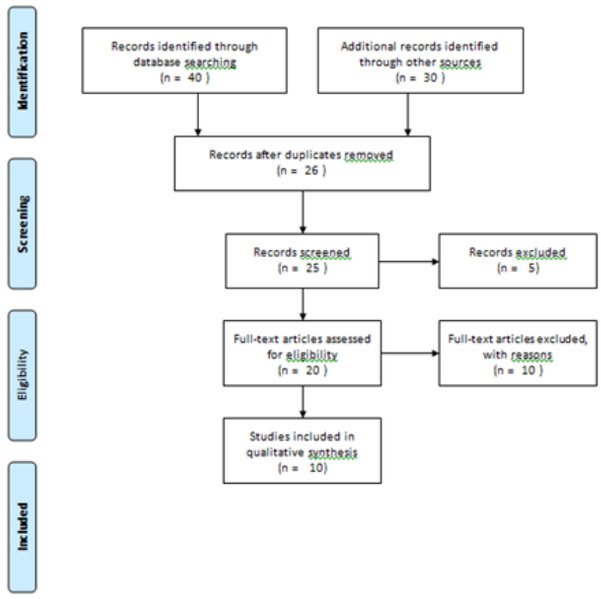

Figure 1. Prisma framework

Sonography is used for its detection as well however there are also options like "three-dimensional computed tomography (3D-CT)". According to the views of Tsuji et al. (2021), 3DCT is a valuable tool in medical science to be used for the augmentation of ultrasonic examination to diagnose skeletal dysplasia [11].

Discussion

The most common cause of this disorder is the mutation in the single cell. However, it needs to mention that fetal skeletal dysplasia comprises around 42 groups containing 436 types of diseases [12]. The mean maternal age of about 32 years when the risks of this disease are considered maximum among pregnant women.

The cases of FSD are quite significant and therefore analysis becomes important. The causes of such skeletal dysplasias concluded from the studies that new mutation within the cell that is not found in the parents that occurred within the fetus of a woman during early pregnancy caused by the baby inheriting two copies from the same defective genes. FSD is a heterogeneous group disease that is difficult to diagnose without proper methods and activities. Diagnosis of these diseases before birth is even more difficult and that is why it is important to make the diagnosis easier to provide recovery to the patients quickly.

As commented by Lian et al. (2021), the most common skeletal dysplasias are thanatophoric dysplasia, achondrogenesis and osteogenesis imperfecta type 2 [13]. Thanatophoric dysplasia is one of the most common dysplasia with an incident rate of 2 to 3 among every 10,000 births. Severe limb shortening is the most common sign of this disease and it also includes frontal bossing, macrocephaly, trident fingers and many more symptoms. In accordance with Deng et al. (2022), these factors also result in pulmonary hypoplasia may lead to respiratory failures [14].

As reflected by Ashwal et al. (2022), the MRI process can be used to diagnose a disease so that patients face fewer difficulties [15]. Poor amplification can also lead to a poor diagnosis of this disease and lack of proper diagnosis can be proved dangerous for pregnant women and the infants that are born with the disease. Traditional microarray and cytogenetic approaches are also can be used to diagnose the FSD [16].

These diseases also show genetic etiology and the diagnosis becomes easier when family history in terms of the medical condition of the family members is known to the doctors.

Abnormal diagnosis becomes more difficult when family history is absent. Therefore, parental medical history can also affect the diagnosis process of the disease.

Improper diagnosis of the diseases due to inefficient parental counselling can result in the emotional burdens of couples affected by the disease in many ways. As opined by Ruzzini et al.

(2021), many of these cases are registered because of parental phenotypes [17]. Lack of family history acts as a constraint in terms of detection of the case of the causes if it is genetic or not [18]. The method of targeted gene sequencing can help in the diagnosis of the disease highly. This sequencing can cover most of the regions and therefore can have a better insight into detecting the disease among fetuses [19].

Clinical manifestations show severe abnormalities, perinatal deaths also occur due to the extreme conditions of this disease. About 23 to 32% of prenatal deaths occur during the first week of the life of infants.

Conclusion

This review provides a deeper understanding of the diagnosis processes of fetal skeletal dysplasia. It evaluates and discusses various research to enlighten the readers about the positive sides and benefits of diagnosis processes of fetal skeletal dysplasia so that the diagnosis processes become easier and more effective. This also improves the overall understanding of the reasons for the development of the mentioned disease. This review also focuses on these reasons and discusses them vividly to improve the overall diagnosis processes related to this disease.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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